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Radiographic Features of Hand Osteoarthritis in Adult Kashin-Beck Disease (KBD): the Yongshou KBD Study

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Abstract

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Author Contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Qiang Fu and Virginia Kraus had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interest statement

No author of this manuscript has any conflict or disclosure that could bias this work including employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and research grants or other funding.

Objective—Kashin-Beck disease (KBD) is a rare and severe osteoarthropathy endemic to China. We evaluated the frequency and patterns of hand radiographic osteoarthritis (rOA) in adults with and without KBD.

Methods—Han Chinese (N=438) from Yongshou County of central China underwent right hand radiography for determining case status. Presence of KBD was based on characteristic radiographic deformities of articular ends of bones including articular surface depression, carpal crowding, any subchondral bone deformities in the proximal end of phalanges or first metacarpal bone, or the distal ends of metacarpal bones 2–5, and any bony enlargement with deformity of the distal ends of phalanges. Hand rOA severity was determined by osteophyte (OST), joint space narrowing (JSN), and Kellgren Lawrence (KL) grades.

Results—This study included 127 KBD and 311 non-KBD adults of similar mean age (39 years) and body mass index (21 kg/m^2). Inter- and intra-rater reliability for radiographic determination of case status and rOA features was high (kappa 0.72–0.96). Compared to non-KBD, KBD adults had significantly more severe hand rOA of the thumb, distal interphalangeal (DIP), proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints. Only KBD adults had end-stage CMC disease. In KBD, DIPs and PIPs were more affected than MCPs and the frequency of osteophytes was significantly higher in PIPs than DIPs.

Conclusions—Compared with age-matched adults from the same area and farming occupation, KBD hand rOA was more widespread and severe, particularly of PIPs and CMCs. The ability to differentiate adult KBD from non-KBD hand rOA will facilitate genetic analyses of the vast majority of affected individuals.

Keywords

osteoarthritis; hand; radiographic; diagnosis; Kashin-Beck Disease

Introduction

Kashin-Beck Disease (KBD) is a rare and severe progressive osteoarthropathy endemic to China [1]. According to the 2013 Chinese Health Statistics document issued by the Chinese Ministry of Health, KBD is still a threat to 38,071,000 people living in KBD endemic areas of China; 16,826 of a total 644,994 KBD affected individuals are children under 13 years old [2]. Geographically, KBD is endemic in a region extending from north-eastern China to the southwest and encompasses 14 of the 34 provinces and regions [3]. Pathologically, KBD affects the epiphyseal cartilage of multiple joints and causes cartilage necrosis of the epiphyseal hypertrophic zone adjacent to subchondral bone; this likely explains the occurrence of severe joint deformities during development in young people with KBD [4]. Radiographic abnormalities associated with KBD can be observed as early as 5 years of age [5]. These radiographic abnormalities reflect secondary repair and remodeling of the adjacent bone and cartilage of the metaphyses and epiphyses in response to cartilage necrosis [6].

After years of persistent research, the pathogenesis of KBD is still unclear. Various causes have been suggested, including: selenium (Se) deficiency alone or in combination with iodine deficiency [7–8]; ingesting of grains with mycotoxins [4]; and excess of fulvic acid,

but none of the proposed explanations is entirely satisfactory [9]. In recent years, more attention has been paid to potential genetic etiologies of KBD [10–12]. The Yongshou KBD study was designed to assess potential genetic etiologies of KBD. The success of genetic studies relies heavily on careful phenotyping of individuals to ascertain their affection status. To date, a standardized and evidence-based system of KBD joint disease evaluation has only been developed for children, as described below, but not adults.

Various Chinese diagnostic criteria for KBD have been available for 16 years [13]. The latest version of the Chinese national diagnostic criteria for KBD [14] was released in 2010. According to these criteria ("Diagnosis of Kashin-Beck Disease", WS/T 207-2010), a diagnosis of KBD is typically based upon a history of living in a KBD area, clinical symptoms, and hand radiographic changes. Based on these criteria, it is generally easy to diagnose KBD in childhood or adolescence. In contrast, it can be difficult to distinguish KBD, particularly mild KBD, from osteoarthritis (OA) in adults. For this reason, some researchers consider the national criteria unsuitable for use in diagnosing adult KBD [15]. The purpose of this study was to define KBD case status based upon hand radiographs and to evaluate the patterns of radiographic features of radiographic hand osteoarthritis (rOA) in a moderately large sample of KBD and non-KBD adults of similar age and occupation.

Materials and Methods

Ethics approval

The Yongshou KBD study is an international collaborative study conducted by permission (document [2007]017) of the Management Office of the Human Genetic Resource Council of the Chinese State. Institutional Review Board (IRB) approval was obtained from Xi'an Jiaotong University (China). In anticipation of sharing samples and clinical data with collaborators, IRB approval was also obtained from Duke University (USA) and the University of North Carolina at Chapel Hill (USA). Written informed consent was obtained from each participant.

Participants

The Yongshou KBD study was conducted in Yongshou County of Shaanxi Province in central China. The selection of participants occurred in three steps. First, the study region (Yongshou County) was selected on the basis of a high KBD prevalence, estimated to be 2.7% according to a government survey conducted in 1979–1982 [5]. Second, to identify a subset of individuals with the most homogeneous environmental exposures for purposes of a future genetic analysis of KBD, one of the 67 villages of Yongshou County (Shangqiu) was selected randomly and every available adult in this village was invited in 2007 to participate in this study; a total of 125 individuals from this village agreed to participate. Permission (document [2007]017) of the Management Office of the Human Genetic Resource Council of the Chinese State was obtained to cover genetic analyses of these 125 individuals. Third, to obtain county-wide data on the hand radiographic presentation of KBD, a total of 1200 adult subjects were selected randomly from among ~60,000 individuals from the remaining 66 villages of Yongshou County. With the assistance of the village leaders, attempts were made to contact all 1200 individuals face to face in 2011; a total of 333 individuals agreed to

participate. These participants were aged 10–12 years at the time of the original government survey.

A total of 458 individuals were enrolled in the study; right hand radiographs could be obtained on 438 (122 from Shangqiu and 316 from all the other 66 villages) and these served as the total sample for these analyses. For both men and women, a total of 96.8% of participants were farmers (98.4% of participants form Shangqiu and 95.6% of the remaining participants).

Radiographs and case definition

Posterior-anterior radiographs of the right hand and wrist were taken using a JF-10 portable X-ray unit (Xianwei Ltd. Co. Shanghai, China). Case status was determined on the basis of radiographic features considered characteristic of KBD (Figure 1). These features were derived from several sources [6] and included four main categories of bone and joint abnormalities: 1) articular surface depressions. These articular depressions appeared both in the absence of other findings of OA but sometimes accompanied them; 2) “carpal crowding,” as described by Wang et al. [6] was a feature considered representative of KBD and not OA; 3) any subchondral bone deformities in the proximal end of phalanges or first metacarpal bone, or the distal ends of metacarpal bones 2–5, such as an irregular subchondral bone surfaces with/without sclerosis, discontinuity or appearance of fragmentation;4) bony enlargement with deformities of the distal ends of phalanges was considered especially characteristic of KBD. Subjects matching any one of the four criteria were classified as KBD. On the basis of these criteria, 127 of the 438 individuals were classified as KBD, 279 had some hand rOA but did not meet the case definition for KBD, and 32 had no evidence for hand rOA.

All radiographs were scored for OST (0–3) and JSN (0–3) using the standardized OARSI atlas (2007) [16], and Kellgren and Lawrence (KL) grade (0–4) [17]. Radiographic scoring (blinded to the age, gender and other characteristics of the subjects) was completed for fifteen joints of the right hand and wrist: four distal interphalangeal joints (DIPs), four proximal interphalangeal joints (PIPs), five metacarpophalangeal joints (MCPs), the thumb interphalangeal (IP) joint, and the first carpometacapal (CMC) joint.

A musculoskeletal researcher (QF) was trained by an expert musculoskeletal radiologists (JBR) to read the hand radiographs for KBD features to determine case status, and radiographic features of hand rOA (OST, JSN and KL grade). Inter-rater reliability for case status determination was made by blinded reading of 50 radiographs by the expert radiologist and the musculoskeletal researcher. Intra-rater reliability for case status determination was made by blinded readings of 100 radiographs by the musculoskeletal researcher on two occasions at least 1½ months apart. Intra-rater reliability of scoring of OA features was made by blinded readings of 30 radiographs (900 OST readings, 450 JSN and KL readings) by the musculoskeletal researcher on two occasions at least 1 ½ months apart. Reliability was assessed by kappa (κ) statistic [18].

Statistical analysis

Hand rOA was defined as OST≥1, JSN≥1 or KL grade≥2. The primary analysis consisted of comparing the mean and standard deviation (SD) of the total number of affected right hand joints comparing KBD and non-KBD subjects by a sample T test. The remaining comparisons were secondary and evaluated by Fisher's exact tests. The frequency of rOA of the thumb joints was analyzed separately. The frequency of rOA of the four fingers was analyzed by row for the three joint groups: DIPs, PIPs and MCPs. The frequency of rOA in individual finger joints was also analyzed; no further statistical analyses of individual joints was pursued if no difference was found by joint group between KBD and non-KBD subgroups. End-stage rOA was defined as OST=3, JSN=3 or KL grade=4. The frequency of end-stage rOA was analyzed for the thumb, the joint groups of the four fingers and for individual joint of the four fingers. We also compared the frequency of OST≥1, JSN≥1 and KL grade≥2 between DIPs and PIPs in the KBD and non-KBD subgroups. All statistical analyses were performed using JMP 9.0.2 (SAS Institute Inc., NC, USA). All tests were two-tailed and a P-value of 0.05 was considered to be statistically significant.

Results

All 438 participants were Han Chinese and 22.8% were female. The mean ± SD age of study cohort was 39.0±3.3 years, and mean ± SD body mass index (BMI) was 21.5±2.2 kg/m^2. The distribution of age, gender and BMI were not significantly different between the total KBD and non-KBD groups (Table 1). The Shangqiu village sample was, on average, a little older (KBD 49.6±10.6 years vs non-KBD 50.5±11.6 years) and with a higher proportion of female participants (KBD 41.7% vs non-KBD 54.8%) than the total sample (Table 1) but also without significant difference by age, gender or BMI (KBD 20.6±2.6 kg/m2 vs non-KBD 21.2±3.0 kg/m2) between the KBD and non-KBD subgroups.

Intra-rater and inter-rater reliability for scoring of the radiographs was high for determination of case status (κ=0.95 and κ=0.72 respectively). Intra-rater reliability for scoring of radiographs OA features was also high (κ=0.92 for OST, κ=0.96 for JSN, κ=0.88 for KL grade).

Most non-KBD individuals (279 of 311 individuals) had some evidence of radiographic hand OA based on the presence of any OST ≥1, any JSN ≥1, or any KL grade ≥1 (Figures 2 and 3). However, the frequency of rOA of the joints of the first digit (thumb IP, MCP and CMC) was significantly greater in the KBD group (Figure 2 A-C). A proportion of both KBD and non-KBD subgroups had some individuals with end-stage hand rOA (OST=3, JSN=3, or KL grade=4) of thumb joints (Figure 2 D-F); no non-KBD subject had end-stage CMC disease while 10.5% (depending on the rOA definition used) of KBD subjects had end-stage CMC OA.

Based on any OST≥1, any JSN≥1 or any KL≥2, the frequency of rOA of the DIPs, PIPs and MCPs joint groups was significantly higher in the KBD group (Figure 3 A-C). In the end-stage rOA, the frequency of rOA of only the DIP and PIP joint groups was significantly higher in the KBD group (Figure 3 D-F). The MCP joint group was less affected than the other two joint groups, and this finding was even more striking in the end-stage rOA (Figure

3 D-F) and in the individual joints. There were no group differences for MCPs of digits 4 or 5 (Supplementary Figure 1A-C).

Comparing KBD and non-KBD subjects, the mean (±SD) number of OA affected joints was greater in KBD subjects: 9.33±2.43 KBD vs. 2.03±0.41 non-KBD (P value <0.0001). Within the KBD group, the frequency of any OST≥1 was significantly greater in PIPs than DIPs (P=0.002); although there was a higher frequency of any JSN≥1 and any KL grade≥2 for PIPs than DIPs in the KBD group, these differences were not statistically significant. In contrast, within the non-KBD group, the frequency of any OST≥1, any JSN≥1 and any KL grade≥2 was slightly higher in DIPs than PIPs but these differences were not statistically significant.

Discussion

A high frequency of rOA of thumb joints was one distinguishing feature of KBD. In addition, end-stage CMC rOA was only observed in KBD cases. In contrast to the non-KBD group, the KBD group had a higher frequency of osteophytes in PIPs than DIPs of the finger joints. This pattern of hand rOA in KBD differed from that of the non-KBD group. A previous study has also observed that in KBD, PIPs were more often affected than DIPs [19]. This finding contrasts with the typical pattern of radiographic hand OA in Western cultures in which DIP involvement of the fingers exceeds the frequency of PIP involvement [20–21].

All study participants were older than 25 years of age. Therefore, we did not use the national Chinese diagnostic criteria for KBD as they are based heavily on hand radiographic features in children, such as abnormalities of the growth plate or epiphyseal plate. The diagnosis of KBD was a global assessment based on the radiographic characteristics of KBD mentioned above. This determination was made by a trained musculoskeletal researcher with high inter-rater agreement with an expert radiologist (JBR) with 25 years experience with OA research image scoring. As expected in adults, we did not observe “coned-shaped epiphyses” and associated physeal irregularities, but rather, subchondral bone deformities of the proximal ends of phalanges or first metacarpal bone, and the distal ends of metacarpal bones 2–5, suggesting the residua of those abnormalities. We used these criteria to diagnose KBD and analyzed the distribution of rOA by joint and joint group in the KBD and non-KBD groups in order to better understand the radiographic patterns of adult KBD hand OA.

In this study, we analyzed the thumb joints separately from the joints of the four fingers because other studies suggested that the thumb joints may reflect different causal mechanisms of OA in comparison with other hand joints [22–23]. This supposition was further supported by a prior study that included principal component analysis [24]. In past studies, patterns of rOA were usually evaluated by row [25], so we analyzed the finger joints by row and the thumb joints by ray. We also analyzed the joint patterns in the severely affected participants (OST=3, JSN=3 or KL grade=4); these individuals are likely to have suffered from KBD since early childhood. For all but the MCPs for which rOA frequency was relatively low, results demonstrated a significantly higher frequency of severe end-stage hand rOA in adults with KBD.

A possible relationship exists between KBD and OA in their pathogenic pathways despite their different etiologies [4]; therefore, KBD could be considered a cause of secondary OA [26]. Comparing KBD with other secondary OA, such as haemochromatosis arthropathy, thyroid achropachy and acromegaly, there are several differences in the epidemiology, localization, severity of symptoms and radiographic changes [27–30]. For instance, two major distinguishing features of KBD, an endemic disease, include its strong association with low Se [31] and the fact that it can affect the epiphyseal plate at a very early age; therefore, the radiographic abnormalities associated with KBD can be observed as early as 5 years old [5, 32]. In contrast, the arthropathy of these other secondary forms of OA typically has their onset in adulthood.

There were two major limitations in this study. First, the Yongshou KBD Study is cross sectional albeit with a moderately large sample size from a KBD endemic area (Yongshou Country) of central China. The findings in this study should be duplicated in a larger sample; receiver operating characteristic (ROC) curve analysis could be applied to establish the gold standard diagnostic criteria for adult KBD. Second, there was a potential unavoidable bias introduced in the random selection of subjects throughout Yongshou County in step 3. We could only track 333 of 1200 individuals randomly selected in 2011 for participation. Those unavailable for interview no longer lived in the original location. It is possible that the subjects remaining in the sampled villages were more likely to suffer from illness of some kind and less able to take on more lucrative work as a laborer in another location.

To our knowledge, there is no effective treatment for adult KBD. However, it is believed that eliminating exposure to potential etiologic agents (for instance toxins and a low Se environment) might slow progression. Moreover, the ability to clearly differentiate adult KBD from non-KBD hand rOA will make it possible to try to identify potential genetic susceptibility loci for KBD in the vast majority of affected individuals. In summary, we evaluated the patterns of hand rOA of KBD and non-KBD adults of similar age, gender, BMI and occupation from a KBD endemic region of central China. In addition to being raised in the same environment, the individuals that were examined all had the same non-obese body habitus. These study features served to minimize selection bias. The distinguishing features of rOA in adults with KBD included more affected joints in the hand and a higher frequency of severe joint involvement, in particular, a higher frequency of PIP OA and severe CMC OA compared with non-KBD subjects. Given that the Chinese national criteria are designed to identify KBD in children, the findings of this study fill a need for diagnostic criteria for KBD in adults that could also promote a better understanding of the pathogenesis of KBD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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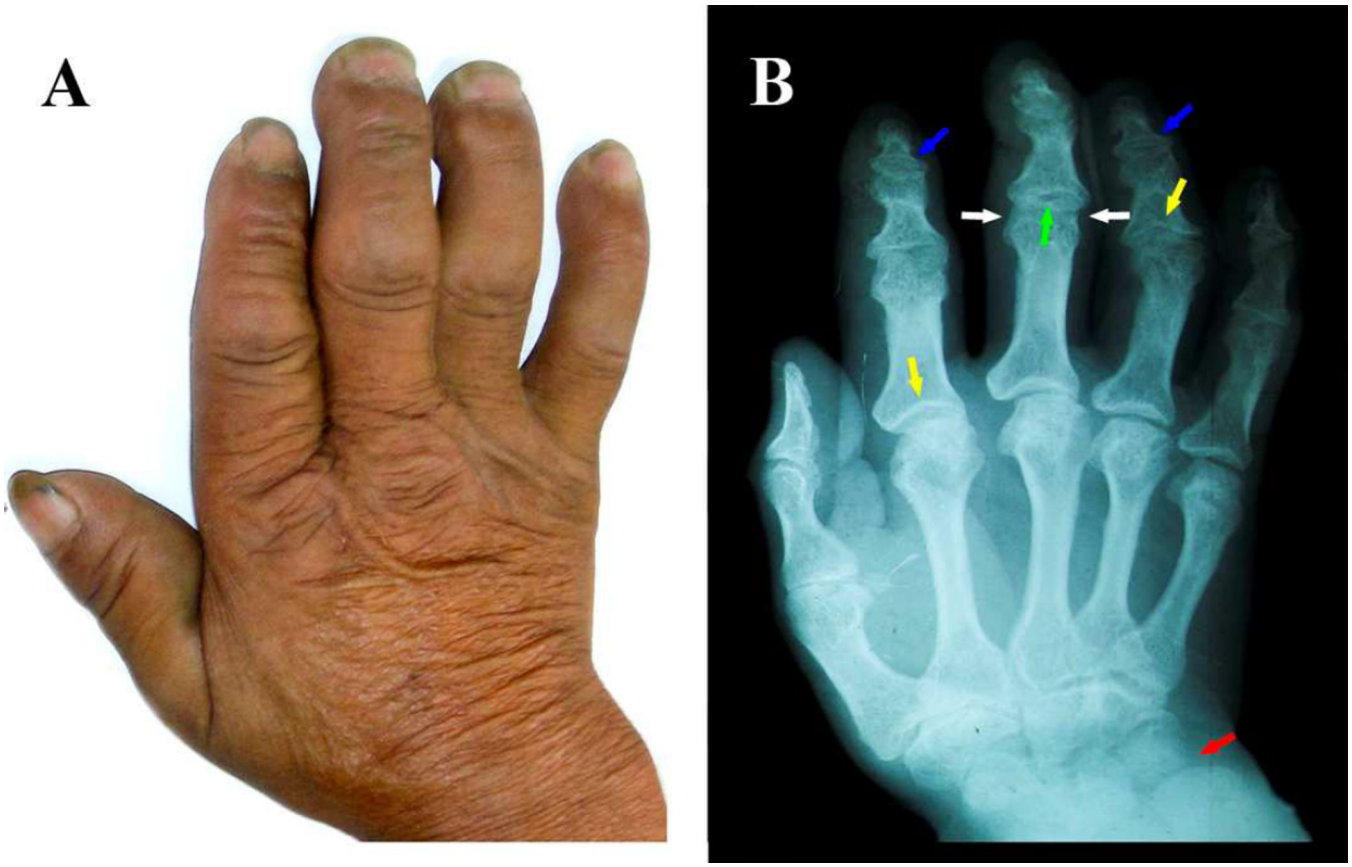

Figure 1. Hand radiographic features of KBD and the four criteria used for diagnosing adult KBD

Right hand of a 55 year old female KBD study participant with brachydactyly (A) and her right hand radiograph (B). The four hand radiographic features used for diagnosing adult KBD are marked with colored arrows: articular surface depression with sclerosis (yellow); “carpal crowding” (red); subchondral bone deformity in the proximal end of the phalanx (blue); and bony enlargement (between white arrows) with deformity of the distal end of phalanx (green).

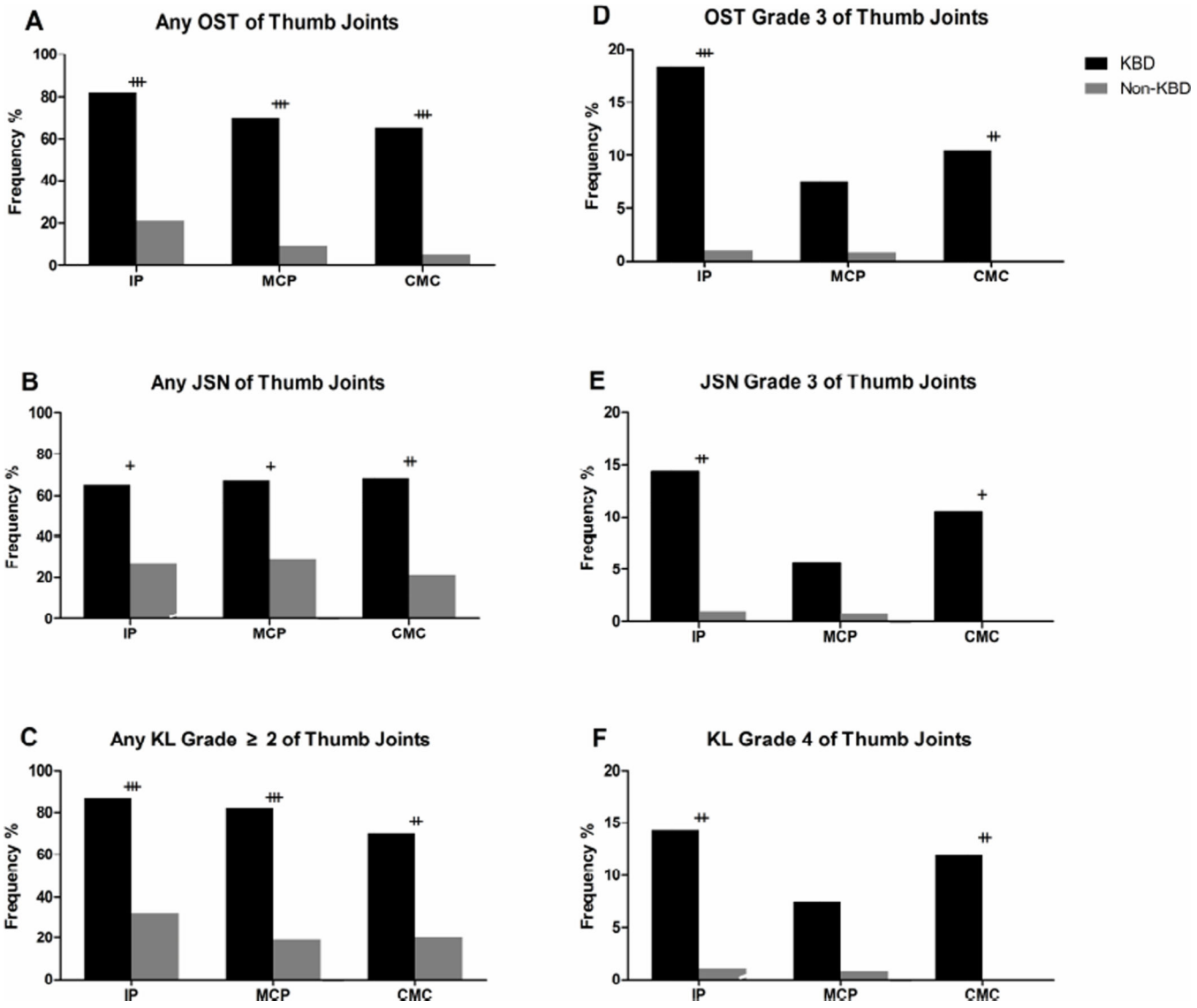

Figure 2. Frequency of radiographic OA features of the joints of digit 1 (thumb) of the hand

The left panels represent the frequency of OST≥1 (A), JSN≥1 (B) and KL grade≥2 (C) in the three joints of digit 1 (thumb). The right panels represent the severely affected subgroups with OST=3 (D), JSN=3 (E) and KL grade=4 (F).

IP, Interphalangeal joint; MCP, metacarpal-phalangeal joint; CMC, carpometacapal joint; All statistical analyses were adjusted for gender, age and body mass index (BMI). +, P value <0.05; ++, P value <0.01; +++, P value <0.001.

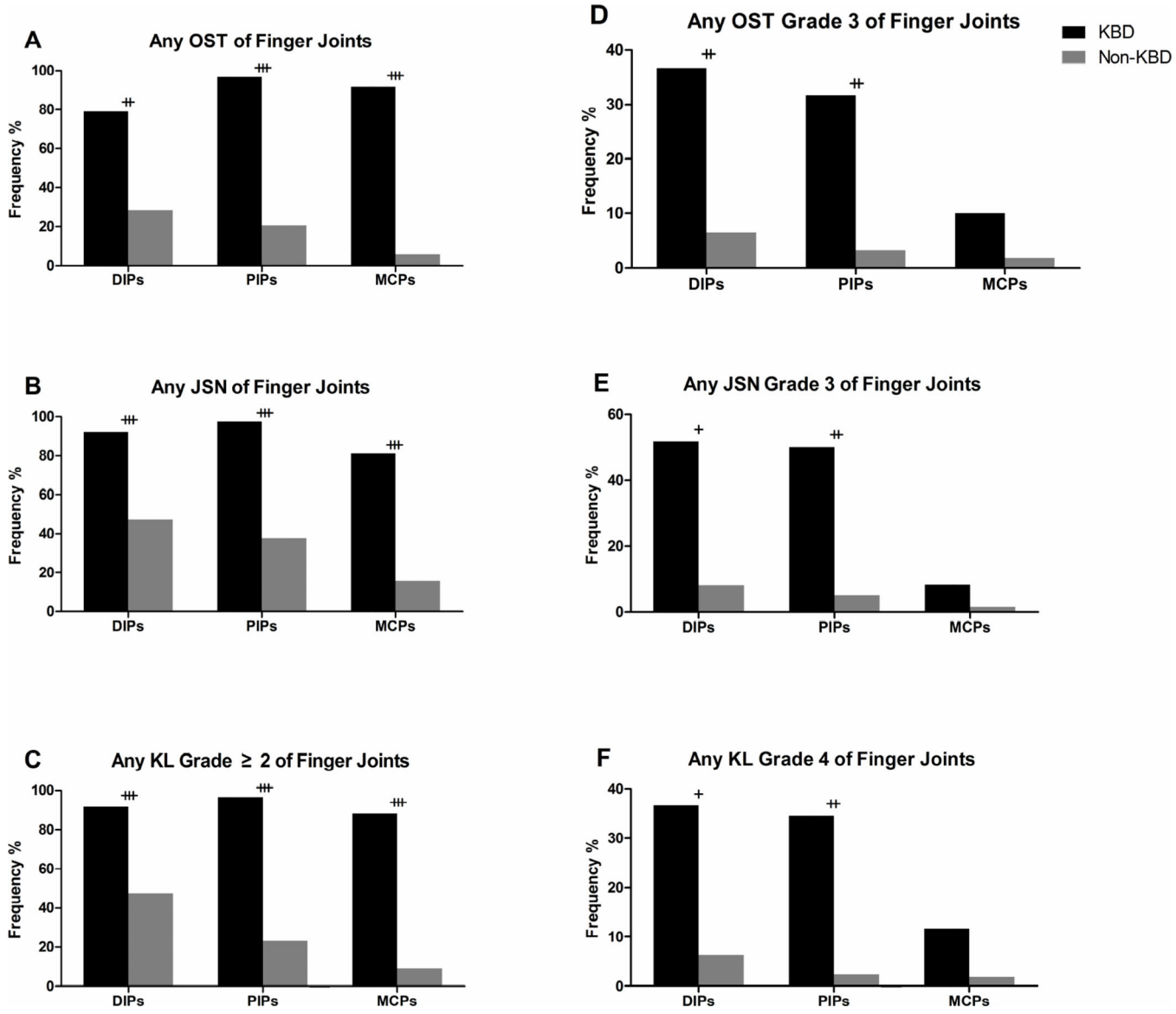

Figure 3. Frequency of radiographic features of the joints of digits 2–5 of the hand

The left panels represent the frequency of any OST≥1 (A), any JSN≥1 (B) and any KL grade≥ 2 (C) in three joint groups: DIPs, PIPs and MCPs of the four fingers (digits 2–5). The right panels represent the severely affected subgroups with any OST=3 (D), any JSN=3 (E) and any KL grade=4 (F).

DIPs, distal interphalangeal joints; PIPs, proximal interphalangeal joints; MCPs, metacarpal-phalangeal joints.

All statistical analyses were adjusted for gender, age and body mass index (BMI). +, P value <0.05; ++, P value <0.01; +++, P value <0.001.

Table 1

Demographics of total study sample.

Participants		KBD Group	Non-KBD Group	P Value
Total Sample	Number	n=127	n=311	
	Age (years)	39.2 ± 3.6	38.7± 3.1	0.15
	Gender (female)	21.3% (n=27)	23.5% (n=73)	0.62
	BMI (kg/m^2)	21.4 ± 1.9	21.6 ± 2.4	0.40

Age and BMI reported mean ± standard deviation.